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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
PROUTY, R

18M2/0722

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ART UNIT	PAPER NUMBER
1814	21

DATE MAILED: 07/22/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 5/24/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-22 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-22 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

Applicant's telephone request for reconsideration of the finality of the rejection of the last Office action is persuasive and the finality of that action is withdrawn.

Applicant's amendments to the claims filed 5/24/93 has been entered.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-22 are rejected under 35 U.S.C. § 103 as being unpatentable over Mullis et al. (Reference AD, U.S. Patent No. 4,683,195) in view of Sutherland et al. and Kaledin et al..

Mullis et al. disclose that amplification of nucleic acids by PCR allows the detection of very rare nucleic acids present in a large excess of other nucleic acids, methods for the amplification of nucleic acids and that detection of amplified nucleic acids is useful for the detection of genetic and

infectious disease. They further disclose that PCR selectively synthesizes only the selected target DNA during amplification.

Sutherland et al. disclose methods for the use of fluorescent dyes including in particular ethidium bromide for measurement of polymerization of nucleic acids. They disclose that these dyes can be provided directly in the polymerization reaction and that the dyes have a greater fluorescence when bound to double stranded DNA than when either bound to single stranded DNA or unbound.

Kaledin et al. show in Table 3 that the minimum concentration of EtBr that inhibits *Thermus flavus* DNA polymerase is 5 μM and that half maximal inhibition requires 23 μM EtBr. Furthermore they teach that this is similar to the results found for other known polymerases. As such one of ordinary skill in the art would not have reasonably expected the levels of EtBr used by Sutherland et al. (1-5 μM, preferably 1.75 μM) to inhibit polymerization by Taq polymerase.

Therefore, it would have been obvious to one of ordinary skill in the art to use the method of detecting polymerization by use of fluorescent dyes during a PCR amplification to detect the target nucleic acid of the amplification reaction because this method is very simple and minimizes sampling and handling errors (see Sutherland et al. column 16, lines 64-69).

In regards to Claim 10, the ordinary skilled artisan would have known that one could quantitate the amount of target DNA

originally present in the amplification reaction from the measured change in fluorescence by a simple comparison to a standard curve of the amount of fluorescence change produced by a given amount of initial DNA.

In regards to Claims 12-16, the use of optic fibers to continuously monitor the fluorescence of a solution is old and well known in the art and as such it would have been obvious to use one in order to monitor the synthesis of the target nucleic acids during the amplification reaction for the added simplicity of not having to remove aliquots of the reaction at various times.

In regards to Claims 17-22, as Sutherland et al. disclose that the fluorescent dye can be provided directly within the starting PCR buffer, it would have been obvious to include the dye within the buffer of a kit for detecting amplified target nucleic acids, such as the one disclosed by Mullis et al. for the added convenience of minimizing the amount of time needed to prepare the reaction.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D., whose telephone number is (703) 308-4000.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RUBERT A. WAX
SUPERVISORY PATENT EXAMINER
GROUP 180